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Effects of Allogeneic Bone Marrow Transplantation On Recipient Bone Mineral Density: A Prospective Study

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ABSTRACT

Allogeneic bone marrow transplant (BMT) recipients have many known risk factors for developing decreased bone mineral density (BMD) after transplantation. We performed a prospective sequential evaluation of BMD in the lumbar spine and nondominant hip using dual-energy x-ray absorptiometry (DEXA) in a cohort of 47 adult patients (median age, 43 years) who were undergoing radiation-based BMT for hematologic malignancies. Baseline DEXA studies were performed before BMT and repeated at 3 to 4 months, 6 to 8 months, and 12 to 14 months after BMT. The majority of patients (60%) had been minimally treated with combination cytotoxic chemotherapy, having received no more than 1 treatment regimen before BMT. Graft-versus-host disease prophylaxis consisted of cyclosporine in combination with either methotrexate or prednisone, or both. Mean lumbar spine and hip BMD were normal before BMT (spine: 1.01 g/cm^2, *z* score = 96%; hip: 0.86 g/cm^2, *z* score = 100%) and gradually decreased (spine: 0.98 g/cm^2, *z* score = 94%; hip: 0.76 g/cm^2, *z* score = 91%) at 12 to 14 months. These declines were statistically significant ($P < .006$ and $< .002$ for lumbar spine; $P < .001$ and $< .001$ for hip). In addition, the sharpest decline occurred during the first 6 months after BMT and was more marked in the hip than the lumbar spine. These data suggest that BMT adversely affects BMD in this patient population.

KEY WORDS

Bone mineral density • Bone marrow transplantation • Leukemia • Lymphoma • Radiation therapy

INTRODUCTION

Allogeneic bone marrow transplantation (BMT) has become an established treatment for a variety of hematologic and nonhematologic disorders [1]. With improvements in survival, the long-term health effects of treatment have become increasingly important. BMT recipients have many risk factors known to be associated with decreased bone mineral density (BMD). However, the presence, extent, and pattern of this problem is only now beginning to be defined in these patients. Previous studies have suggested that the use of steroids or immunosuppressants, exposure to radiation and chemotherapy, premature gonadal failure, and previous treatment of malignancy all contribute to non–age-related loss of BMD [2,3]. Safe, sensitive methods to detect subtle changes in BMD have recently become more readily available, allowing accurate prospective quantification of the extent of this problem after BMT [4-6].

This article reports the results of a prospective protocol of sequential measurement of nondominant hip and lumbar spine BMD by dual energy x-ray absorptiometry (DEXA). Patients were scanned before, and at regular intervals after, sibling and matched unrelated donor allogeneic BMT. All transplants were performed to treat hematologic malignancies in a cohort of 47 patients by the Department of Hematology and Bone Marrow Transplantation at the City of Hope National Medical Center (COHNMC), Duarte, CA.

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PATIENTS AND METHODS

Patients

Study subjects consisted of 47 patients treated at the COHNMC Bone Marrow Transplant Unit between March 1995 and September 1998. They were enrolled for up to 4 weeks before undergoing a fractionated total-body irradiation (fTBI)-based conditioning regimen for allogeneic or matched unrelated donor BMT as treatment for a hematologic malignancy. To be eligible for the study, patients had to (1) undergo BMT for acute myeloid or lymphoid leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma, or myeloproliferative or myelodysplastic disorders; (2) receive an HLA-identical sibling or unrelated donor BMT; (3) receive a radiation-based preparatory regimen; and (4) be at least 30 years old. A full medical history was obtained from all patients. Close attention was paid to medications known to affect BMD and to the menopausal status of female patients. Patients with pre-existing disorders known to decrease BMD (eg, hypophosphatemic rickets, Cushing syndrome, hyperparathyroidism, vitamin D deficiency, ethanol abuse, liver cirrhosis, and hyperthyroidism) were considered ineligible. The study was approved by the Institutional Review Board at COHNMC.

Preparatory Regimen and Transplantation

Patients received 1 of 2 previously described radiation-based preparative regimens [7,8]. Twenty-six patients received fTBI, 1320 cGy (120 cGy per fraction for a total of 11 fractions on days –8 through –5), in combination with 60 mg/kg per day of cyclophosphamide (CY) on days –4 and –3. Twenty patients received 1320 cGy fTBI and 60 mg/kg VP-16 on day –3. The remaining patient received fTBI 1200 cGy (120 cGy per fraction for 10 fractions) in combination with VP-16 60 mg/kg on day –4 and CY 100 mg/kg on day –2.

Twenty-five patients (53%) received freshly collected marrow on day 0 from an HLA genotypically identical sibling donor. Twenty-two patients (47%) received HLA-matched unrelated donor marrow. All marrow grafts were unmanipulated and infused immediately after collection, except for the removal of red blood cells or plasma in cases of major or minor ABO incompatibility, as previously described [9].

Graft-Versus-Host Disease Prophylaxis

Thirty-six patients (77%) received a previously described combination of cyclosporine (CSA), methotrexate (MTX), and prednisone (PSE), and 9 patients (19%) received CSA-MTX without PSE [10]. CSA was given by continuous intravenous (IV) infusion, 5 mg/kg per day, as a loading dose starting on day –2; reduced to 3 mg/kg per day on day 4; and increased to 3.75 mg/kg per day from day 15 to 35. Thereafter, patients received 5 mg/kg of oral CSA twice a day until day 83, followed by a tapering dose until day 180. MTX was administered IV at a dose of 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6; methylprednisolone was started on day 7 at 0.25 mg/kg IV twice a day and doubled to 0.5 mg/kg IV twice a day on day 15. At the time of discharge, all patients were switched to oral PSE, which was then slowly tapered from day 29 until day 180. The CSA-MTX schedule was as mentioned above, with the addition of 1 extra dose of MTX 10 mg/m^2 IV on day 11. One patient received CSA-PSE only. One syngeneic transplant recipient did not receive graft-versus-host disease (GVHD) prophylaxis.

Supportive Care

All patients were housed in single rooms with high-efficiency particulate air filtration systems. Infection prophylaxis also included gut decontamination, which was accomplished with oral nonabsorbable antibiotics, oral levofloxacin, oral trimethoprim-sulfamethoxazole, and a strict low-bacteria diet, all starting on approximately day –8. A reverse isolation technique with masks and gowns was used when patients' neutrophil count fell below 500/μL. Broad-spectrum antibiotics were used for the first febrile episode, and all patients received prophylactic low-dose amphotericin (0.15 mg/kg per day) or fluconazole (100 mg twice a day) starting on day 1, as described [11,12].

All blood products were irradiated with 2500 cGy before infusion. Patients who were seropositive for cytomegalovirus (CMV) or who received a bone marrow graft from a CMV-seropositive donor underwent bronchoalveolar lavage (BAL) on day 35. When a patient's BAL or blood culture result was positive for CMV, the patient received prophylactic gancyclovir, as previously described by our group [13]. All patients who were seropositive for herpes simplex virus also received acyclovir prophylaxis, 250 mg/m^2 every 12 hours, beginning on day –1 and continuing until day 21 after BMT.

Patients were not routinely given growth factors (eg, recombinant human granulocyte colony-stimulating factor). Red blood cell transfusions were given to maintain a hematocrit >25%, and platelet transfusions were administered for platelet counts <20 × 10^3/μL or as clinically indicated for acute bleeding.

Bone Mineral Density

BMD was measured by a DEXA technique using a Hologic QDR-2000 densitometer (Hologic, Waltham, MA). Measurements of the lumbar spine and nondominant hip were made at 4 time points: before BMT (baseline) and at 3 to 4 months, 6 to 8 months, and 12 to 14 months after BMT. This technique has a precision of within 0.5%. Well-established normal values for BMD, stratified by age and sex, are available from the manufacturer, and thus a control group was not required. BMD was measured in grams per square centimeter, with results also expressed as *t* scores (the deviation from predicted peak bone mass) and *z* scores (the deviation from the age- and sex-matched control population).

Statistical Methods

Descriptive statistics were tabulated for all relevant patient characteristics known to influence BMD. Initial BMD scan measurements were taken for all 47 patients before BMT to obtain a stable baseline estimate and ensure that baseline levels were similar when the smaller cohort with follow-up scans was analyzed. To maximize the sample size for comparing each post-BMT scan with baseline scans, paired *t* tests were calculated using all available data for each time point. To account for the 3 multiple comparisons being

Table 1. *Patient Characteristics Related to Bone Mineral Density (n = 47)**

	n	%
Age at bone marrow transplantation, y†		
30-39	16	34
40-49	24	51
≥50	7	15
Ethnicity		
European-American	38	81
African American	2	4
Asian-American	5	11
American Indian	2	4
Sex		
Male	32	68
Female	15	32
Menopausal status of female patients		
Postmenopausal	4	27
Premenopausal	11	73
Prior combination cytotoxic chemotherapy		
Yes	19	40
No	28	60
Prior use of medications known to affect bone density		
Yes	10	21
No	37	79
Diagnosis and status at BMT		
Acute lymphoblastic leukemia/acute myelogenous leukemia	13	28
Myelodysplastic syndrome	3	6
Chronic myelogenous leukemia (chronic phase)	24	51
Non-Hodgkin's lymphoma	4	9
Myelofibrosis/myeloproliferative disorder	3	6
Transplant type		
Matched sibling donor	25	53
Matched unrelated donor	22	47
Conditioning regimen		
fTBI/CY	26	55
fTBI/VP-16	20	43
fTBI/VP-16/CY	1	2
Graft-versus-host disease prophylaxis		
CSP/MTX	9	19
CSP/MTX/PSE	36	77
CSP/PSE	1	2
None	1	2

*CSP indicates cyclosporine; CY, cyclophosphamide; fTBI, fractionated total body irradiation; MTX, methotrexate; PSE, prednisone.
†Median age 43 years (range, 31-54 years).

made in this set of analyses, the alpha level was adjusted to .0167 using the conservative Bonferroni method. The repeated measures analysis of variance (ANOVA) procedure was then used to test for overall mean differences across the first 3 BMD scan time points with complete data available on 18 patients. The Duncan multiple comparison test was used to identify those means that differed significantly when the overall P value was found to be significant in the ANOVA analysis. The Mantel-Haenszel χ^2 test was used to test for the percentage of patients demonstrating osteopenia (t score –1.0 to –2.5) or osteoporosis (t score < –2.5) over the first 3 time points for the cohort of 18 patients with complete doses. Multivariate regression analysis was then conducted for those patients to determine whether type of donor (sibling/matched unrelated), use of BMD-affecting medications (yes/no), previous chemotherapy (yes/no), or fTBI/CY conditioning regimen (yes/no) were significant predictors of change in BMD measures from baseline to 6 to 8 months after BMT. Change was calculated as an absolute difference in the scores. These analyses were conducted using two-sided tests, with .05 as the level of significance. All statistical procedures were conducted using SAS software, version 6.12 (SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics

The clinical characteristics of the study population are shown in Table 1. The median age of recipients at the time of BMT was 43 years (range, 31-54). The majority (81%) of the patients were of European-American descent. Fifteen patients (32%) were female, 4 of them postmenopausal at the time of BMT. Ten patients (21%) had used medications known to affect BMD. Thirty of the patients (64%) underwent transplantation for chronic myeloproliferative disorders, and 28 (60%) had received no more than 1 cytotoxic combination chemotherapy regimen (ie, for induction of acute leukemia or treatment of non-Hodgkin's lymphoma) before BMT. The number of patients who underwent matched sibling BMT was approximately equal to that who underwent unrelated donor BMT, and all patients received a radiation-based conditioning regimen. Forty-six patients (98%) received CSA, 45 (96%) received MTX, and 37 (79%) received PSE for GVHD prophylaxis. The median follow-up time for surviving patients was 21 months (range, 12-39 months). Of the original cohort of 47 patients, 33 were able to complete at least 1 scan after BMT. The other 14 patients died from BMT-related complications or disease progression at a median of 100 days (range, 30-170 days) after BMT.

Bone Mineral Density

The mean lumbar spine and hip BMD, z scores, and t scores were close to normal at baseline and gradually decreased after BMT, as shown in Table 2. Results of the paired t test mean comparisons of BMD and z scores show that for patients who finished a specific scan, this decline was highly significant when that scan was compared with the baseline scan. Furthermore, Tables 3 and 4 show declining mean BMD measurements over time, with statistically significant mean differences from baseline found at the 3- to 4-month, 6- to 8-month, and 12- to 14-month scan time points. The multiple comparison of means for the 12 patients who completed all 4 scans shows a decline in z scores, with the decline more marked in the nondominant hip (104% to 93% [$P < .001$]) than in the lumbar spine (98% to 94% [$P = .033$]) (Figure 1 and Table 4). This corresponds to mean drops in nondominant hip and lumbar spine BMD of 0.11 g/cm^2 and 0.04 g/cm^2, respectively. In addition, multiple comparisons of means of nondominant hip BMD, z scores, and t scores suggest that the most rapid decline, a mean of 0.09 g/cm^2, 10% and 9%, occurred in the first 6 months after BMT; by comparison, a mean decline of 0.02 g/cm^2, 1% and 2%, respectively) occurred in the 6 to 12 months after BMT (see Table 4).

Table 2. *Changes in Bone Mineral Density After Bone Marrow Transplantation (BMT)**

	At Baseline		3-4 Months Post-BMT		6-8 Months Post-BMT		12-14 Months Post-BMT		
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	P†
Anteroposterior lumbar spine									
Bone density, g/cm²									
Before BMT	47	1.01 ± 0.12	26	1.01 ± 0.12	21	1.04 ± 0.11	21	1.04 ± 0.11	—
After BMT									
3-4 mo			26	0.98 ± 0.13	18	0.99 ± 0.12	17	1.00 ± 0.11	.001
6-8 mo					21	0.99 ± 0.11	14	0.99 ± 0.12	.002
12-14 mo							21	0.98 ± 0.13	.006
z Score, %									
Before BMT	47	96.1 ± 11.5	26	96.4 ± 11.3	21	98.9 ± 10.7	21	99.1 ± 10.9	—
After BMT									
3-4 mo			26	93.2 ± 12.7	18	95.1 ± 11.8	17	94.7 ± 11.3	.002
6-8 mo					21	94.6 ± 10.9	14	94.6 ± 12.1	.003
12-14 mo							21	94.4 ± 13.0	.002
t Score, %									
Before BMT	47	93.8 ± 11.1	26	93.9 ± 10.8	21	96.5 ± 10.1	21	97.0 ± 10.2	—
After BMT									
3-4 mo			26	90.7 ± 12.3	18	92.7 ± 11.4	17	92.4 ± 10.5	.002
6-8 mo					21	92.2 ± 10.4	14	92.2 ± 11.0	.003
12-14 mo							21	91.8 ± 12.1	.001
Hip									
Bone density, g/cm²									
Before BMT	47	0.86 ± 0.13	26	0.88 ± 0.12	21	0.89 ± 0.12	21	0.88 ± 0.09	—
After BMT									
3-4 mo			26	0.83 ± 0.13	18	0.86 ± 0.13	17	0.82 ± 0.13	.001
6-8 mo					21	0.81 ± 0.13	14	0.80 ± 0.14	.001
12-14 mo							21	0.76 ± 0.12	.001
z Score, %									
Before BMT	47	100.2 ± 13.3	26	102.8 ± 13.4	21	103.9 ± 12.4	21	103.4 ± 11.7	—
After BMT									
3-4 mo			26	97.0 ± 14.8	18	99.9 ± 13.7	17	95.8 ± 15.1	.001
6-8 mo					21	94.7 ± 13.9	14	94.1 ± 15.5	.001
12-14 mo							21	90.5 ± 15.0	.001
t Score, %									
Before BMT	47	92.7 ± 13.1	26	94.7 ± 13.0	21	95.9 ± 12.4	21	96.0 ± 11.4	—
After BMT									
3-4 mo			26	89.2 ± 13.9	18	92.4 ± 13.0	17	88.4 ± 13.9	.001
6-8 mo					21	87.2 ± 13.3	14	86.7 ± 14.3	.001
12-14 mo							21	83.5 ± 13.4	.001

*Four scan data points were not included owing to out-of-range scan dates.

†Paired *t* test comparing the mean value for the subset of patients who finished a specified scan with their baseline mean.

When the clinically meaningful end points of osteopenia (*t* score = −1.0 to −2.5) and osteoporosis (*t* score < −2.5) were combined and evaluated, there was a gradually increasing trend after BMT from the 3- to 4-month time point to the 12- to 14-month time point in the proportion of patients developing these disorders at the lumbar spine and hip (from 19% and 14% before BMT to 38% and 47%, respectively) (Figures 2 and 3).

Univariate regression analyses were conducted to determine significant predictors of change in BMD measures from baseline to 3 to 4 and 6 to 8 months after BMT at the hip and spine. The independent variables used for this analysis included type of donor (syngeneic, sibling, or matched unrelated), use of BMD-affecting medications (eg, thyroid hormone, glucocorticoids, anticoagulants, lithium, anticonvulsants, tetracyclines, CSA, antacids containing aluminum, and gonadal hormones), previous chemotherapy, sex, menopausal status of females, and type of conditioning regimen. None of the clinical factors evaluated by univariate analysis for measurements taken at the spine were found to be significantly predictive of BMD decline. For measurements taken at the hip, the factor found to be significantly predictive for a decrease in BMD was chemotherapy before BMT ($P < .05$). Given the small sample sizes, however, this finding may be spurious. Further investigation is necessary to explore this relationship and enable a multivariate model to be developed.

DISCUSSION

This prospective study of patients who had normal bone mass before BMT demonstrated that there was a statistically significant (and, by *t* score assessment, clinically relevant)

Table 3. *Changes in Bone Density After Bone Marrow Transplantation (BMT): Comparison of Means for Patients Receiving First 3 Scans (n = 18)*

	Mean ± SD	Overall P Value*	Multiple Comparison†
Lumbar spine			
Bone density, g/cm²		.014	
Before BMT	1.03 ± 0.11		A
After BMT			
3-4 mo	1.00 ± 0.12		B
6-8 mo	0.99 ± 0.12		B
z Score, %		.016	
Before BMT	97.9 ± 11.0		A
After BMT			
3-4 mo	95.1 ± 11.8		B
6-8 mo	94.3 ± 11.3		B
t Score, %		.018	
Before BMT	95.4 ± 10.0		A
After BMT			
3-4 mo	92.7 ± 11.4		B
6-8 mo	91.9 ± 10.6		B
Hip			
Bone density, g/cm²		<.001	
Before BMT	0.89 ± 0.13		A
After BMT			
3-4 mo	0.86 ± 0.13		B
6-8 mo	0.81 ± 0.14		C
z Score, %		<.001	
Before BMT	104.1 ± 13.3		A
After BMT			
3-4 mo	99.9 ± 13.7		B
6-8 mo	95.0 ± 15.0		C
t Score, %		<.001	
Before BMT	96.3 ± 13.3		A
After BMT			
3-4 mo	92.4 ± 13.0		B
6-8 mo	87.7 ± 14.3		C

*Repeated-measures analysis of variance.
†For values with the same letter, means are not significantly different based on the Duncan multiple range test ($\alpha = .05$).

Table 4. *Changes in Bone Density After Bone Marrow Transplantation (BMT): Multiple Comparison of Means for Patients Receiving All 4 Scans (n = 12)*

	Mean ± SD	Overall P Value*	Multiple Comparison†
Lumbar spine			
Bone density, g/cm²		.022	
Before BMT	1.02 ± 0.11		A
After BMT			
3-4 mo	1.00 ± 0.12		A B
6-8 mo	0.99 ± 0.12		B
12-14 mo	0.98 ± 0.15		B
z Score, %		.033	
Before BMT	98.3 ± 12.6		A
After BMT			
3-4 mo	96.1 ± 12.8		A B
6-8 mo	94.8 ± 12.5		B
12-14 mo	93.8 ± 16.1		B
t Score, %		.023	
Before BMT	95.7 ± 11.3		A
After BMT			
3-4 mo	93.5 ± 11.8		A B
6-8 mo	92.3 ± 11.1		B
12-14 mo	91.1 ± 14.5		B
Hip			
Bone Density, g/cm²		<.001	
Before BMT	0.89 ± 0.11		A
After BMT			
3-4 mo	0.85 ± 0.13		A B
6-8 mo	0.80 ± 0.15		B C
12-14 mo	0.78 ± 0.15		C
z Score, %		<.001	
Before BMT	104.2 ± 13.7		A
After BMT			
3-4 mo	99.3 ± 15.5		A B
6-8 mo	94.4 ± 16.8		B C
12-14 mo	93.1 ± 17.6		C
t Score, %		<.001	
Before BMT	96.5 ± 13.7		A
After BMT			
3-4 mo	91.8 ± 14.5		A B
6-8 mo	87.2 ± 15.5		B C
12-14 mo	85.7 ± 16.0		C

*Repeated-measures analysis of variance.
†For values with the same letter, means are not significantly different based on the Duncan multiple range test ($\alpha = .05$).

decrease in mean BMD over the 12- to 14-month observation period after transplantation. The decrease was more marked in the hip (approximately 11%) than in the lumbar spine (approximately 4%). Furthermore, bone mass loss was more rapid in the first 6 months than in the second 6 months after BMT, especially in the hip (9.3% in the first 6 months compared with 3.6% in the second 6 months).

Until recently, reliable noninvasive techniques to accurately measure BMD have not been widely available. The availability of DEXA has greatly improved the reliability and accuracy of BMD measurement without having to expose patients to the hazards of earlier, more invasive techniques such as quantitative tomography [4,5]. Despite this advance, this study was difficult to complete because of the considerable mortality and morbidity associated with allogeneic sibling and unrelated donor BMT: 33 of the original cohort of 47 patients completed at least 1 scan after BMT but only 12 underwent all 4 planned scans.

Non–age-related loss of BMD has been associated with many factors that play a role in BMT: the use of glucocorticoids, loss of gonadal function, inactivity, radiation therapy, chemotherapy, and CSA use [2,3]. Loss of bone mass has also been demonstrated in recipients of cardiac and other organ transplants [14], and cross-sectional studies have suggested that BMD is reduced in survivors of BMT [14-17]. However, the magnitude, timing, and pattern of this problem after BMT is only now beginning to be defined by prospective studies such as this one and those of Ebeling et al. [18] and Välimaki et al. [19].

The present study differs from the studies of Välimaki et al. and Ebeling et al. in that our study population consisted predominantly of patients who underwent only allogeneic (sibling or unrelated donor) transplantation and, perhaps more importantly, had been minimally treated with combination cytotoxic chemotherapy before BMT. This may account for the near-normal mean BMD in our patients before BMT,

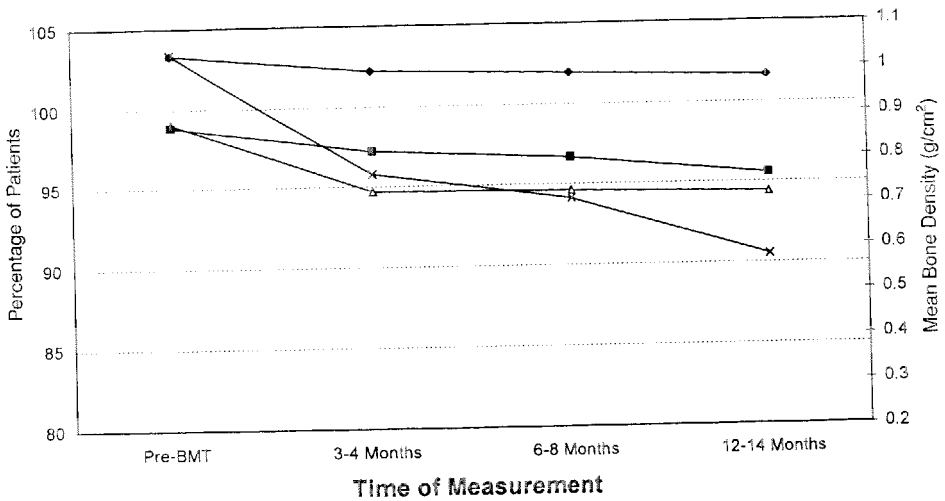

Figure 1. *Changes in mean bone density measurements over time in patients who underwent 4 scans after bone marrow transplantation (BMT) (n = 12). △ indicates anteroposterior (AP) lumbar spine z score (%); ◆, AP lumbar spine bone density (g/cm²); x, nondominant hip z score (%); ■, nondominant hip bone density (g/cm²).*

compared with the impaired baseline BMD of the subjects in the other 2 published prospective studies. Thus, in our study, any changes in BMD after transplantation can be more clearly attributed to the BMT procedure rather than the ongoing effects of pre-BMT factors. The present study is in keeping with the study of Välimaki et al. [19] in that the majority of bone loss occurred in the first 6 months after transplantation. However, unlike the patients in the study by Välimaki et al., our patients exhibited continuing bone loss—albeit at a lower rate—in both the nondominant hip and lumbar spine beyond 6 months after BMT. In the study by Välimaki et al. [19], female patients were treated with estrogen therapy relatively early after BMT. This, in addition to differences in the degree of pre-BMT chemotherapy, may partially account for the discrepancy in BMD results in the patient populations of the 2 studies.

In our study, because of the loss of bone mass over the 12 to 14 months after BMT, the combined proportion of patients developing the clinically significant disorders of osteopenia and osteoporosis grew from 19% at baseline to 38% at 14 months after BMT as measured in the lumbar spine, and from 14% to 47% as measured in the hip. Similar findings have been seen in previous studies of patients who had been treated with chemotherapy before BMT [19,20]. This finding, in our minimally treated patient population, again supports the concept that BMT is the major contributing factor to this clinically important problem.

The prevalence of osteonecrosis of the hip has been estimated to be 5% to 10% at 5 years after BMT [21-25]. Our study, in keeping with the BMD study of Ebeling et al. [18], shows that the loss of bone mass is greater in the hip than in the lumbar spine. The bulk of this loss occurs in the first 6 months after BMT, when patients are receiving relatively higher doses of steroids and CSA for GVHD prophylaxis. It is known that glucocorticoids suppress bone formation and increase bone resorption, whereas CSA causes high-turnover bone loss with both increased resorption and enhanced bone formation [26-28]. The upper femur contains more cortical bone than the lumbar spine [19]. Cortical bone, in contrast to trabecular bone, is affected by CSA as well as corticosteroids [29], which may account for the increased reported incidence of osteonecrosis and, in our patients, the higher degree of osteoporosis/osteopenia at this site.

Few data are available regarding therapeutic intervention aimed at improving BMD in BMT patients. In 1 study, hormone replacement therapy after BMT increased bone mass by 5% in 13 women who started treatment an average of 13 months after BMT [30]. The study of Välimaki et al. [19] showed that prophylactic use of calcitonin, calcium supplements, or both had no beneficial effect on BMD in post-BMT patients.

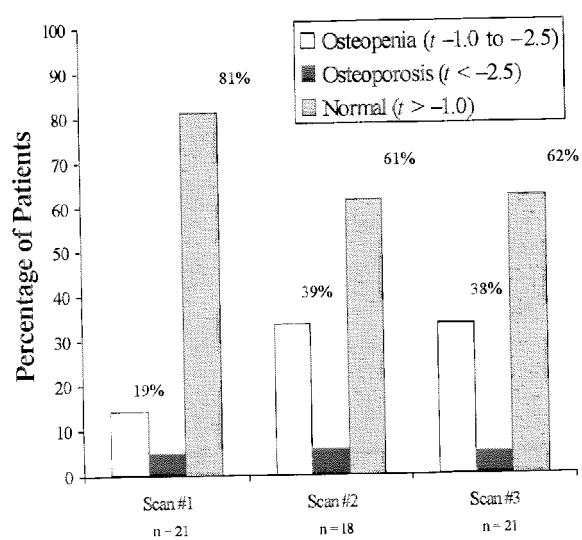

Figure 2. *Percentage of patients experiencing osteopenia or osteoporosis in the anteroposterior lumbar spine. Data are for patients with 3 or more scans completed (P = .62).*

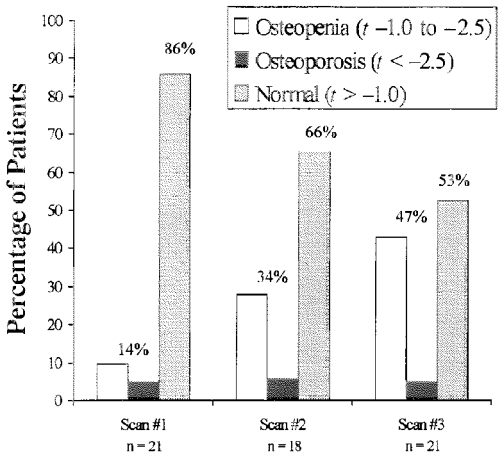

Figure 3. *Percentage of patients experiencing osteopenia or osteoporosis in the nondominant hip. Data are for patients with 3 or more scans completed (P = .19).*

In conclusion, this prospective study confirmed that there is a non–age-related loss of BMD after BMT. The extent of the loss is clinically significant even in patients with relatively normal bone mass before BMT, which suggests that BMT itself, rather than pre-BMT risk factors (eg, underlying leukemia), plays a major role. The most rapid loss occurs during the first 6 months after transplantation, and the hip is affected more than the lumbar spine. This clinically important problem could potentially be prevented by simple prophylactic measures (eg, resumption of weight bearing as soon as possible after BMT) that have proved successful in cardiac transplantation patients [31]. Hormone replacement therapy could also be initiated early after BMT. Other pharmacologic therapies, such as the use of bisphosphonates, that have been shown to be beneficial in solid organ transplant recipients are also worthy of further investigation [32].

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